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ORIGINAL REPORT

Phase II Evaluation of Pemetrexed in the Treatment of Recurrent or Persistent Platinum-Resistant Ovarian or Primary Peritoneal Carcinoma: A Study of the Gynecologic Oncology Group

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
To estimate the antitumor activity of pemetrexed in patients with persistent or recurrent platinum-resistant epithelial ovarian or primary peritoneal cancer and to determine the nature and degree of toxicities.

Patients and Methods
A phase II trial was conducted by the Gynecologic Oncology Group. Patients must have had cancer that had progressed on platinum-based primary chemotherapy or recurred within 6 months. Pemetrexed at a dose of 900 mg/m^2 was to be administered as an intravenous infusion over 10 minutes every 21 days. Dose delay and adjustment was permitted for toxicity. Treatment was continued until disease progression or unacceptable adverse effects.

Results
From July 6, 2004, to August 23, 2006, 51 patients were entered. A total of 259 cycles (median, four; range one to 19 cycles) of pemetrexed were administered, with 40% of patients receiving six or more cycles. Overall, the treatment was well tolerated. More serious toxicities (grade 3 and 4) included neutropenia in 42%, leukopenia in 25%, anemia in 15%, and constitutional in 15% of patients. No treatment-related deaths were reported. One patient (2%) had a complete and nine patients (19%) had partial responses, with a median duration response of 8.4 months. Seventeen patients (35%) had stable disease for a median of 4.1 months. Eighteen patients (38%) had increasing disease. Three patients (6%) were not assessable. Median progression-free survival was 2.9 months, and overall survival was 11.4 months.

Conclusion
Pemetrexed has sufficient activity in the treatment of recurrent platinum-resistant ovarian cancer at the dose and schedule tested to warrant further investigation.

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INTRODUCTION

Contemporary management of ovarian cancer involves aggressive tumor cytoreductive surgery followed by platinum-based multiagent chemotherapy, to which 70% of patients will manifest a response.[1] Unfortunately, most of these patients' disease will recur. Subsequent responses are modest and of short duration.[2] Two prognostic groups have been described based on their likelihood of response to re-treatment with platinum.[3] This "resistant" group is those who experience disease progression while being treated with primary platinum therapy or who experience recurrence shortly after their initial response. The Gynecologic Oncology Group (GOG) has been evaluating new agents in the phase II setting in this group of patients with resistant disease.[4-14]

Pemetrexed (Alimta, LY231514, Eli Lilly, Indianapolis, IN) is an antifolate, antineoplastic agent that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication.[15] In vitro studies have shown that pemetrexed inhibits thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase, all folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides.[15] Pemetrexed has demonstrated activity in multiple tumor types, including mesothelioma, non–small-cell lung cancer (NSCLC), and breast, colorectal,

pancreas, bladder, and head and neck cancers.[16-18] Pemetrexed in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.[19] As a single agent, it is indicated for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy.[18] Recent phase II trials in patients with cervical cancer suggest possible activity for pemetrexed.[20,21]

The objectives of this trial were to estimate the antitumor activity of pemetrexed in patients with persistent or recurrent platinum-resistant epithelial ovarian or primary peritoneal cancer and to determine the nature and degree of toxicity of pemetrexed in this cohort of patients.

PATIENTS AND METHODS

Patients must have had histologically confirmed recurrent or metastatic epithelial ovarian cancer or primary peritoneal cancer. Histologic diagnosis was confirmed by review of the GOG Pathology Committee. Their disease must have been considered platinum-resistant or refractory according to standard GOG criteria (treatment-free interval after platinum-based therapy of less than 6 months or progression during platinum-based therapy). Patients must have had, and were allowed to receive, no more than one prior platinum-based chemotherapeutic regimen, containing carboplatin, cisplatin, or another organoplatinum compound, for management of primary disease. All patients must have had measurable disease, defined as lesions that could be measured by physical examination or by means of medical imaging techniques. Patients must have had at least one target lesion that could be used to assess response on this protocol as defined by Response Evaluation Criteria in Solid Tumors. Tumors within a previously irradiated field will be designated as nontarget lesions. Ascites, pleural effusions, or CA-125 levels were not to be considered measurable disease. Patients must have had a GOG performance status of 0 to 2. They must have recovered from effects of recent surgery, radiotherapy, or chemotherapy, and at least 3 weeks must have elapsed since any prior therapy directed at the malignant tumor. They were to be free of significant infection. To be enrolled, patients must have had adequate bone marrow function, with a WBC count $\geq$ 3,000/μL, platelets $\geq$ 100,000/μL, and granulocytes $\geq$ 1,500/μL; adequate renal function with a creatinine level of $\leq$ 2.0 mg; hepatic function with bilirubin of $\leq$ 1.5$\times$ the institutional norm and AST and alkaline phosphatase $\leq$ 3$\times$ the institutional norm. Patients with another malignancy before entering study or a concomitant malignancy other than skin (excluding melanoma) were ineligible. This project received local institutional review board review and approval. Patients provided written informed consent consistent with federal, state, and local requirements before receiving protocol therapy.

Pemetrexed at a dose of 900 mg/m^2 was to be administered as an intravenous infusion over 10 minutes every 21 days. Patients who had prior radiotherapy were treated at a one dose level reduction of 700 mg/m^2. Seven days before initiation of pemetrexed, patients were to begin taking folic acid at a dose of 350 to 600 μg daily as well as receive an intramuscular injection of 1,000 μg of vitamin B_{12}. Dexamethasone 4 mg administered orally twice a day was taken the day before, the day of, and the day after each dose of pemetrexed.[22] Nonsteroidal anti-inflammatory drugs were held for the 2 days before and after pemetrexed administration. CBCs were obtained weekly. Cycles were to be repeated every 21 days pending an absolute neutrophil count more than 1,500/mL, platelet count more than 1,000/mL, and resolution of nonhematologic toxicities. Weekly delays in therapy were prescribed to allow resolution of persistent hematologic and nonhematologic toxicity. However, patients were removed from the study for delays in excess of 2 weeks. Dose reduction was required for febrile neutropenia and/or grade 4 neutropenia persisting for more than 7 days, grade 4 thrombocytopenia, or grade 2 bleeding, and greater than grade 2 peripheral neuropathy. Prophylactic growth factors were not allowed unless patients experienced recurrent neutropenic complications after prescribed treatment delays. Use of erythropoietin was allowed. Patients were treated until disease progression or intolerable toxicity precluded further treatment.

Statistical Design

The study used a two-stage accrual design with an early stopping rule in the event that the treatment demonstrated insufficient activity.[23] During the first stage of accrual, 19 to 26 patients were to be entered and evaluated. If at least three responses were observed among the first 19 to 25 patients, or at least four responses in 26 patients, a second phase of accrual was to be initiated, which would increase accrual to 44 to 51 patients. The regimen would be considered active if at least seven responses were observed among 44 to 45 patients or at least eight responses were observed among 46 to 51 patients. If the true response rate is 10%, the average probability of designating the treatment as active is limited to 10%. Conversely, if the true response rate were 25%, then the probability of correctly classifying the treatment as active would be 90%.

RESULTS

From July 6, 2004, to August 23, 2006, 51 patients were entered by 15 member institutions of the GOG. Two patients were ineligible (wrong primary, low creatinine clearance), and one did not receive treatment and were not included in the analysis. Response could not be assessed in three treated patients; however, these patients are included in the determination of response rate. The characteristics of this patient population are summarized in Table 1. The majority of patients entered onto the study had serous and/or poorly differentiated (grade 3) histology and a GOG performance status of 0. All patients had platinum-refractory or resistant disease as specified in the protocol. One patient had received prior radiotherapy. The median time to progression or recurrence after initial platinum-based chemotherapy was 9 months, and the median platinum-free interval was 3 months, with a range of 0 to 6 months.

A total of 259 cycles (median, four cycles; range one to 19 cycles) of pemetrexed were administered, with 40% of patients receiving six or more cycles. Patients were compliant with their vitamin premedication regimens. As anticipated, the primary adverse event was hematologic (Table 2). More serious toxicities (grade 3 and 4) included neutropenia in 42%, leukopenia in 25%, anemia in 15%, and constitutional in 15%. The median WBC nadir for those 36 patients experiencing leukopenia was 2,245/μL (range, 800 to 3,700/μL). The median platelet nadir count for those 26 patients experiencing thrombocytopenia was 86,000/μL (range, 13,000 to 149,000/μL). Seven patients were removed from study because of toxicity. No treatment-related deaths were reported. Pemetrexed was associated with a favorable nonhematologic safety profile (Table 2). The most frequent serious nonhematologic adverse events were constitutional (15%), neurologic (10%), and infection (10%). There was minimal renal toxicity.

The antitumor activity of pemetrexed is summarized in Table 3. One patient (2%) had a complete and nine patients (19%) had partial responses, with a median duration response of 8.4 months (range, 2.0 to 45.1+ months) and an overall response rate of 21% (10 of 48 patients; 95% CI, 10.5% to 35.0%). An additional 17 patients (35%) experienced stable disease for a median of 4.1 months, whereas 18 patients (38%) experienced disease progression while receiving therapy. Three patients (6%) were not assessable. The median progression-free survival was 2.9 months (range, 1.0 to 33.1 months), and overall survival was 11.4 months (range, 1.6 to 34.4 months).

Table 1. Patient Characteristics

Characteristic	No. of Patients
Age, years	
< 40	1
40-49	6
50-59	14
60-69	14
70-79	11
> 79	2
Performance status	
0	30
1	15
2	3
Race	
White	47
Black	1
Cell type	
Serous	34
Clear cell	5
Mixed epithelial	6
Endometrioid	1
Adenocarcinoma, unspecified	1
Undifferentiated carcinoma	1
Grade	
1	1
2	15
3	31
Unspecified	1
Prior chemotherapy	48
Prior radiotherapy	1
Courses	
1	3
2	15
3	3
4	8
5	0
> 5	19

Table 2. Adverse Events

	Grade				
Adverse Event	1	2	3	4	Total
Leukopenia	11	13	11	1	48
Thrombocytopenia	15	5	2	4	48
Neutropenia	9	6	11	9	48
Anemia	14	17	7	0	48
Transfusion	0	1	0	0	48
Coagulation	0	1	0	0	48
Gastrointestinal	14	14	4	0	48
Nausea/vomiting	15	7	4	0	48
Genitourinary	4	0	2	0	48
Hepatic	2	2	1	0	48
Alopecia	7	5	0	0	48
Dermatologic	10	10	3	0	48
Neurologic	12	1	4	1	48
AST	9	4	0	0	48
Alkaline phosphatase	3	3	0	0	48
Ocular	2	3	1	0	48
Hemorrhage	2	0	1	0	48
Pulmonary	4	1	0	0	48
Lymphopenia	1	0	0	0	48
Constitutional	17	14	5	2	48
Metabolic	20	9	4	0	48
Cardiovascular	3	0	0	0	48
Pain	8	6	1	1	48
Infection	2	5	5	0	48
Auditory	0	2	1	0	48
Lymphatics	4	1	0	1	48
Endocrine	2	0	0	0	48
Allergy	0	1	0	0	48

NOTE. No treatment-related deaths have been reported. The median WBC count for those 36 patients experiencing leukopenia was 2,245/μL (range, 800 to 3,700/μL). The median platelet count for those 26 patients experiencing thrombocytopenia was 86,000/μL (range, 13,000 to 149,000/μL).

DISCUSSION

With the recognition of differentiation in response rates to platinum re-treatment based on time to recurrence after primary platinum therapy, the GOG undertook a series of phase II protocols to evaluate new agents, dosing strategies, or combinations that might have activity in patients with platinum-resistant recurrent ovarian or primary peritoneal cancer. An active agent or agents so identified would be appropriate for evaluation in frontline trials, as was done in GOG 182.[24] The results of several of these prior GOG trials have been published.[4-14] Responses were observed in 27% of patients treated with oral etoposide, 22% of patients treated with docetaxel, and 21% of those treated with weekly paclitaxel, whereas others showed limited or no activity (Table 4).[10,14,25]

Pemetrexed (Alimta, LY231514) is an antifolate antineoplastic agent that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication.[15] It contains a pyrrolopyrimidine-based nucleus that exerts its antineoplastic activity by disrupting folate-dependent metabolic processes essential for cell replication. In vitro studies have shown that pemetrexed inhibits thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase, all folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate-binding protein transport systems. In ovarian cell lines, internalization of folate is more dependent on the reduced folate carrier than the folate receptor α.[26,27] Once in the cell, pemetrexed is converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase.[28] The polyglutamate forms are retained in cells and are inhibitors of thymidylate synthase and glycinamide ribonucleotide formyltransferase.[15] Polyglutamation is a time- and

Table 3. Response

Response	No. of Patients	%
Complete response	1	2
Partial response	9	19
Stable disease	17	35
Increasing disease	18	38
Not assessable	3	6
Total	48	100

Table 4. Response Rates and 95% CIs for Single Agents in Selected Phase II GOG Trials

Study	Agent	Response Rate				PFS (months)	
		No. of Patients With Response	Total No. of Patients	%	95% CI (%)	Median	Range
26LL[25]	Oral etoposide	11	41	27	14.2 to 42.9	5.7	0.8-30.8+
126C[5]	Altretamine	3	30	10	2.1 to 26.5	2.4	0.4-154.8+
126D[6]	Pyrazoloacridine	2	24	8	1.0 to 27.0	2.2	0.7-24.3
126G[8]	CI-958	1	25	4	0.1 to 20.4	1.5	0.5-15.4
126H[9]	24-hr topotecan	1	25	4	0.1 to 20.4	2.1	0.3-29.6
126I[11]	9-aminocamptothecin	8	56	14	6.4 to 26.2	2.9	0.5-46.0
126J[10]	Docetaxel	13	58	22	12.5 to 35.3	2.1	0.5-26.2
126K[12]	Oxaliplatin	1	23	4	0.1 to 21.8	1.7	0.6-13.1
126M	Epothilone-B	7	50	14	5.8 to 26.7	4.4	0.8-32.6+
126N[14]	weekly paclitaxel	10	48	21	10.5 to 35.0	4.8	0.6-62.2+
126Q	Pemetrexed	10	48	21	10.5 to 35.0	2.9	1.0-33.1

Abbreviations: GOG, Gynecologic Oncology Group; PFS, progression-free survival.

concentration-dependent process that occurs in tumor cells and, to a lesser extent, in normal tissues. Polyglutamate metabolites have an increased intracellular half-life that results in prolonged drug action in malignant cells.[22] Initial phase I trials without folate or vitamin B_{12} supplementation showed a maximum-tolerated dose of 500 to 600 mg/m^2.[29] Pemetrexed administered as a single agent once every 21 days at 500 to 600 mg/m^2 has demonstrated activity in multiple tumor types, including mesothelioma, NSCLC, and colorectal, pancreas, bladder, head and neck, and cervical cancer.[16-20] Preliminary data from a trial in South Africa indicated a 21% response rate in patients with chemotherapy-naive cervical cancer.[20] Patients treated in these early studies did not receive folic acid or vitamin B_{12} supplementation. Pemetrexed is approved for the treatment of mesothelioma and NSCLC. On the basis of multivariate analyses of toxicities observed in several pemetrexed trials, all patients receiving pemetrexed were subsequently supplemented with dietary folic acid (350 to 1,000 μg) and vitamin B_{12} (1,000 μg, administered as an intramuscular injection) to decrease the frequency of severe hematologic and nonhematologic toxicity.[30,31] Subsequent phase I trials with folate and vitamin B_{12} supplementation have shown doses of more than 1,000 mg/m^2 to be tolerated.[32-34]

The GOG has conducted phase II trials of pemetrexed at 900 mg/m^2 administered intravenously with folate and vitamin B_{12} supplementation in cervical (GOG0127T) and endometrial (GOG0129O) cancers, in addition to the present study.[21] The 900-mg/m^2 dose was selected on the basis of the phase I trials with folate and vitamin B_{12} supplementation and the concern that supplementation might compromise activity. Two recent trials in breast cancer and NSCLC found no response advantage for pemetrexed doses greater than 500 mg/m^2.[35,36] A second phase II study of single-agent pemetrexed in patients with platinum-resistant ovarian cancer examined the efficacy and safety of doses of 500 mg/m^2 and 900 mg/m^2 administered once every 21 days (H3E-MC-JMHF, conducted by Eli Lilly). Pemetrexed had activity equivalent to that of other approved agents in platinum-resistant disease; however, in the absence of any apparent dose response, the 500 mg/m^2 dose had the preferable toxicity profile.[37]

In this trial, pemetrexed was well tolerated, with mild and noncumulative toxicity, and exhibited activity more favorable than that seen in other agents that have been tested in first-line combinations by the GOG. The response rates in patients with platinum-resistant disease of the agents selected for inclusion in GOG 182 were topotecan, 6.5% to 12.4%; liposomal doxorubicin, 12%; and gemcitabine, 13% to 14%.[38-40] Pemetrexed has sufficient activity in the treatment of recurrent platinum-resistant ovarian cancer at the dose and schedule tested to warrant further investigation. Thus it should be considered for combination with other agents, especially carboplatin, in first-line therapy. Trials in other tumor sites show that pemetrexed can be combined with both cisplatin and carboplatin.[41-48] A single-institution phase II trial of pemetrexed and carboplatin in platinum-sensitive recurrent ovarian cancer reported an overall response rate of 61%: one complete response (2%), 24 partial responses (59%), 14 cases of stable disease (34%), and two cases of progressive disease (5%). Median time to progression was 4.6 months (95% CI, 3.2 to 5.9 months), whereas median PFS was 7.7 months (95% CI, 6.7 to 10.1 months). It was concluded that carboplatin and pemetrexed is a well-tolerated regimen with significant activity in platinum-sensitive recurrent ovarian cancer.[49] In addition, pemetrexed seems to be synergistic with bevacizumab in some tumor cell lines and in vivo.[50-52] A phase I trial of pemetrexed, carboplatin, and bevacizumab for NSCLC showing its feasibility was also presented at the annual meeting of the American Society of Clinical Oncology.[53] Another potential role for pemetrexed is in consolidation or maintenance therapy. Postinduction maintenance therapy with pemetrexed was well tolerated and offered superior progression-free survival compared with placebo in patients with advanced NSCLC.[54]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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